E-cigarettes: Learnings for inhalation scientists

How studying e-cigarette technology may lead to new inhalation therapies

Philip Chi Lip Kwok
University of Hong Kong

Philippe Rogueda
Aedestra Limited

Lu Hou
University of Hong Kong

Why should we look at electronic cigarettes?

Electronic cigarettes (ECs) or e-cigarettes are devices that produce aerosols through heating and vaporizing solutions called e-liquids, which may or may not contain nicotine.[1] The inhalation of aerosols generated from ECs is colloquially called "vaping" so ECs are also termed "vaping devices." Most are currently marketed for recreational use. Some have even been approved as smoking cessation aids.

ECs share a common purpose with conventional pharmaceutical inhalation devices: they produce aerosols intended to be orally inhaled into the respiratory tract. However, ECs are much cheaper and more popular than pharmaceutical inhalers, as evident from their widespread recreational use. They seemingly serve the same goal of pulmonary delivery so it is worthwhile to examine ECs from the viewpoint of inhalation drug development and explore what can be learned from them.

History of ECs

Although the origin of the EC is still controversial, its invention in 2003 has been popularly attributed to a Chinese pharmacist named 韓力, pronounced Hon Lik in Cantonese or Han Li in Putonghua.[2] By 2007, ECs had expanded into the American market where their development and popularly increased rapidly.[3] One popular justification for the use of nicotine-containing ECs is that they might assist in smoking cessation because EC aerosols are cleaner and less harmful than tobacco smoke.[4] Clinical studies on the effectiveness of ECs in smoking cessation are few and their results are best described as inconclusive. Nicotine-containing ECs appeared to be better than placebo ECs for long-term smoking cessation.[5] Their effectiveness was once proven to be comparable to that of transdermal patches.[5] However, due to the small number of trials, the findings are inconclusive and confidence in them is low. Currently, most globally marketed EC devices are manufactured in mainland China.[6] Their manufacture is subjected to lower levels of regulation and quality control than for pharmaceutical inhalers.

EC designs

ECs are available in many different sizes and designs. The common ones are similar to a tobacco cigarette or pen in appearance but the market has been moving rapidly to tank systems, described below. Despite the diversity in design, they share the same components and operation principles. The basic design includes a mouthpiece, an indicator light, an e-liquid cartridge or reservoir, a heating element (e.g., a metal coil with high resistance) and a battery. For ECs with cartridges, the e-liquid is prefilled into the cartridges by the manufacturer. These cartridges are replaceable but not refillable. On the other hand, ECs with reservoirs can be refilled by the user with any e-liquid. In fact, users can mix their own e-liquids instead of purchasing ready-made formulations (e.g., preparing homemade solutions containing nicotine, flavoring or even marijuana). The heating element and the cartridge or reservoir are collectively known as the atomizer.[3,7,8]

Three generations of designs

ECs can be classified into three generations, according to their stage of evolution and design complexity. The first

generation ECs are called "cigalikes" or "e-hookahs" (EHs) and are quite simple. They look similar to tobacco cigarettes and employ e-liquid cartridges so their atomizers are called "cartomizers." There are two types of ECs: disposable and reusable. The former have non-rechargeable batteries and must be disposed of entirely when their power has run out, whereas the latter have rechargeable batteries.[9]

Second generation ECs are called "eGos." They may have cartridges or refillable reservoirs. All of them have rechargeable batteries with high power storage capacity (350-1300 mAh) and can be charged via a universal serial bus (USB) connector. They may have more sophisticated components such as a puff counter or a switch for changing the voltage supplied to the heating element. These were the first ECs to have adjustable battery power. The variable voltage is used to control the frequency and duration of the generated puffs.[2] EGos are pen-like and larger than cigalikes due to their larger batteries. In the case of refillable reservoirs, the atomizers are called "clearomizers" because the reservoirs are transparent, which makes it convenient for the user to monitor the e-liquid level. The heating element in older eGo designs is situated near the mouthpiece, on top of the clearomizer. In later designs, the heating element is situated below the clearomizer, further from the mouthpiece to lower the temperature of the aerosol.

Third generation ECs are called "mods" or "tanks." They employ higher capacity batteries and have a wider range of control over the electronic variables that modulate aerosolization and aerosol temperature. The battery is usually shaped as a palm-sized rectangular block with digital displays and switches.[3]

Operating principles

The operating principles are largely similar for all ECs. A user inhales through the mouthpiece; power is supplied to the heating element to heat the e-liquid; the e-liquid is soaked from the reservoir into a wick that is in contact with the heating coil. Heating can be triggered by an internal airflow sensor that detects the inhalation airflow or by an external manual switch. The temperature of the heating element depends on its construction material and electronic variables such as voltage and power. The heating coil of some ECs have been reported to reach temperatures of 65-120°C, much lower than the combustion temperature in cigarettes.[10, 11] The heating coil is not in direct contact with the liquid. The heated e-liquid will evaporate and travel through the mouthpiece. In general, there is a single air path over the heater, with cooling in the space post-heater. In some designs, ambient air is channeled into the mouthpiece during inhalation through small holes on the sides of the ECs that maintain the airflow and pressure drop. Upon cooling, the e-liquid vapor condenses into droplets that are inhaled. To mimic the action of smoking a tobacco cigarette and to indicate a puff is delivered, many ECs have light emitting diode (LED) indicator lights that are switched on simultaneously with the heating element.[12, 13]

E-liquids: An excipient cocktail

E-liquids are solutions comprised of a solvent vehicle and solutes. The solvent base can be a mixture of glycerin, propylene glycol, ethanol and water. The solutes include nicotine and food flavorings. Several hundred flavors are available on the market, ranging from conventional (e.g., fruits, chocolate, menthol) to exotic ones (e.g., bubble gum, butterscotch, gourmet cinnamon, pie crust and root beer). E-liquids may or may not contain nicotine, just as they may or may not contain all four solvents listed above.

Most e-liquids are manufactured in China, the United States and Europe.[6] Since regulation requirements for e-liquids are relatively loose, the labeling of the identity and quantity of their ingredients are often unclear or even erroneous. For example, the United States Food and Drug Administration (FDA) has reported the detection of nicotine in e-liquid cartridges that were labeled as nicotine-free.[11] The proportion of the solvents in the e-liquids are often not disclosed. Glycerin and/or propylene glycol usually constitute the major solvent vehicle and can occupy more than 90% of the formulation by mass because they are essential for generating the aerosols. Interestingly, these two liquids are popularly used for producing artificial fogs and smokes for theatrical effects.[14]

Although glycerin and propylene glycol are generally regarded as safe (GRAS) and have been approved for use in oral medications, they have not been approved in any inhaled pharmaceutical products. It is known that aerosolized propylene glycol can irritate the airways even though it is non-toxic.[15, 16] Since ECs are marketed for recreational use, there are numerous varieties of e-liquids containing a diverse range of flavorings and different nicotine strengths to assuage the cravings of "vapers." Most of the flavoring agents (74%) are diacetyl and/or acetyl propionyl compounds that have been approved for food products but whose effects after inhalation are unknown.[17, 18] It should be noted that the data presented in reference 17 came from selectively tested "sweet flavorings" such as toffee, chocolate, caramel, etc., because they were believed to be more likely to contain such compounds.

We believe other flavored e-liquids should be analyzed in a more comprehensive study. In addition, some e-liquid manufacturers make bold claims, such as: "Our E-flavors aren't just safer, they taste better, and give you more bang for your buck. They are the only flavor concentrates on the market engineered specifically for inhalation."[19] Toxicity, especially chronic toxicity of inhaled flavoring agents from ECs, should also be investigated thoroughly before such agents can be claimed safe.

EC performance and aerosol properties

Aerosols produced from ECs are popularly misnamed as "vapors." Vapors should only contain a single phase (i.e., gas only). However, ECs produce droplets dispersed in a gas (air) so these aerosols should be more properly called "fogs" or "smokes."[20-22] Some solid particles may also be produced from the heating of the heating coil and wick. Although the proportion of liquid droplets and solid particles is unknown, it is expected that the aerosol consists

mostly of droplets of carrier liquid: glycerin, propylene glycol, etc.

The exact partitioning of nicotine and the flavorings between droplets and vapors has rarely been measured. In one study, the diameter of the droplets/particles generated from two unnamed commercial ECs were in the nanometer range (250-450 nm), comparable to those produced from tobacco cigarettes.[23] The small droplet size suggested they should deposit in the deep lungs. The aerosols in the study were sampled and measured by a differential mobility spectrometer coupled to a smoking-cycle simulator.[23]

In another study, the volumetric droplet size distributions of aerosols generated from a Kimree V12 EC, measured by laser diffraction, were between 1-10 μm, with minimal nano-sized droplets.[24] While droplets < 5 μm would be expected to enter the lungs, the larger ones may deposit in the oropharynx and be absorbed buccally or swallowed. The difference between the two studies, in the measured droplet size range, could be due to differences in the testing setup, experimental procedure and/or the EC model. The relationship between droplet size distribution or dose output and the physicochemical properties of the formulation has not been studied for ECs.

The performance and aerosol properties of ECs vary widely due to their difference in designs. In a study of four brands of cartridge-based ECs,[20] aerosol density between puffs varied depending on the brand. The minimum airflow rate to produce aerosols ranged from 4-21 mL/s with pressure drops of 0.2-1.5 kPa. The tested ECs would continuously puff between 250-300 times over the life of the cartridges. The pressure drop tended to increase over the period of use, especially near the end of the cartridge life for some brands. There were inter- and intra-brand variations in EC performance, indicating poor quality control in the manufacture of these products.

These observations agree with those from another study of nine disposable ECs and e-hookhas. EHs are physically and mechanically similar to ECs but their e-liquids have lower nicotine concentrations and different flavors. The products that were activated manually by a switch required a lower airflow rate (3 mL/s) to produce aerosols than those that were breath-activated (4-17 mL/s). The former produced fewer puffs (about 200 puffs) than the latter ones (more than 300 puffs) when used continuously until product exhaustion. There was high inter- and intra-product variation in aerosol density, as reflected in the aerosol spectrophotometric absorbance at 420 nm (0.41-0.84 absorbance).[25] Video examination showed that tobacco cigarettes produced shorter puff duration, on average, than ECs (2.4 s vs. 4.3 s).[26]

A study that analyzed the actual use of two brands of ECs by human subjects found that the mean puff duration was 2.65 s/puff and the volume of aerosol per puff was 51 mL. During a 10-minute smoking session, most subjects took more than 20 puffs at an airflow rate of 20 mL/s and a peak airflow rate of 27 mL/s.[27]

Another study compared the pressure drop and aerosol density of four brands of ECs and eight brands of tobacco cigarettes. Overall, the vacuum required for aerosol generation (i.e., pressure drop) by ECs (1.15-1.5 kPa for three brands) were higher than that of tobacco cigarettes (0.3-0.8 kPa for eight brands). The pressure drop of a fourth brand of EC in this study was particularly low, at only 0.25 kPa. The aerosol density varied between brands but was reproducible between puffs over the first 10 puffs for a given brand of EC or tobacco cigarette. However, after this initial stage of product life in the ECs, aerosol density decreased and pressure drop increased with usage. On the other hand, these two parameters were relatively stable for tobacco cigarettes.[21]

A study of commercial EC products has shown that over the course of 300 puffs, the total amount of aerosolized nicotine was 0.5-15.4 mg, with the most effective delivery within the first 150-180 puffs.[28] It was also found that only 50-60% of the nicotine stored in the EC cartridges could be aerosolized.[28] However, the amount of nicotine deposited at the various sites along the respiratory tract was not determined in this study. The deposition of EC aerosols in the lungs has not been directly measured (e.g., by scintigraphy) but one pharmacokinetic study showed that 99.6, 94.8, and 98.3% of the nicotine, glycerin and propylene glycol, respectively, inhaled from a range of ECs were systemically retained.[29] These data show that ECs are efficient delivery systems.

Users report satisfaction of their nicotine cravings and tasting of flavorings. However, it is not clear where the absorption occurs. Are the compounds absorbed through the buccal mucosa in the mouth or the respiratory epithelium in the lungs? The uncertainty about the partitioning of substances between droplets and vapors makes prediction of the deposition site(s) difficult without experimental data. Thus, future studies should investigate the mode and location of absorption of EC aerosols.

How toxic are EC aerosols?

Until now, there has been no evidence that short-term use of ECs is linked with health risk.[5] In addition, the long-term physiological effects of inhalation of the excipients, glycerin, propylene glycol and flavorings are unknown because they have not been evaluated in controlled clinical studies. Many of these compounds are not yet approved for inhalation. However, studies on the effects of inhaled glycerin and propylene glycol conducted on animals have shown relatively low toxicity.[30-32] It should be noted that these studies investigated acute toxicity rather than chronic toxicity from repeated exposure over long periods of time, which is closer to the mode of exposure in EC users. Some of these excipients may undergo chemical change or degradation to produce potentially toxic chemicals upon heating during aerosolization.[33] For example, propylene glycol can change to propylene oxide, which is a carcinogen, and glycerin to acrolein, which is an irritant.[2,34] Besides these, formaldehyde-containing hemiacetals have also been identified from heated e-liquids containing propylene

glycol and glycerin.[35] They may also release formaldehyde (a known carcinogen). The heat-degradation of the numerous flavoring agents in ECs has also not been studied.[34]

Nicotine can undergo thermal and photolytic degradation to yield harmful chemicals. Commercial e-liquids have been found to contain tobacco-specific nitrosoamines including N-nitrosonicotine, N-nitrosoanabasine, N-nitrosoanatabine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.[11] In fact, cartridges that were labelled as nicotine-free were found to contain tobacco-specific nitrosamines and impurities such as diethylene glycol, cotinine, anabasine, myosmine, and ß-nicotyrine.[11] Other nicotine-related degradants found in heated e-liquids include nicotinecis-N-oxide, nicotine-trans-N-oxide and anatabine.[36] The United States and European Pharmacopeias specify the maximum allowable levels of nicotine-related impurities because these compounds are also present in products containing nicotine, such as patches and chewing gums for smoking cessation.

While the ingredients in the original e-liquids may seem relatively harmless (even though their effects after inhalation is largely unclear), the major concern is about the degradants that are generated through heating during aerosolization. Thus, monitoring of the long-term effects of inhaled EC aerosols is needed.

How safe are ECs in consumers' hands?

Due to variations in regulation and manufacturing standards, EC products can pose potential safety issues. For nicotine-containing e-liquids, the risk of leakage from cartridges/reservoirs or spillage from refill bottles can cause nicotine poisoning by dermal exposure.[37] The accidental ingestion of the e-liquid may cause harm or even death, as the acute minimum lethal oral dose of nicotine is 6.5-13 mg/kg for adults.[38] That means 22-45 mL of an e-liquid containing 20 mg/mL nicotine (the maximum concentration for an e-liquid regulated by the European Union)[39] is needed to reach this minimum lethal oral dose for a 70 kg adult. This dose is expected to be lower for children, who may be more prone to accidentally ingesting e-liquids.

In addition to safety concerns about nicotine, the potential leachables and extractables resulting from contact between the e-liquid and the various components in the ECs are not routinely reported. The internal components of ECs are made with a wide range of materials, including metals, plastics, rubber and ceramics.[40] Physicochemical interactions between the additives and these materials may result in the presence of potentially toxic leachables and extractables in the e-liquid. These compounds may be inhaled unintentionally with potential adverse effects in the airways. Heavy metal (aluminum, chromium, iron, nickel, silver, and tin) and silicate particles have been found in aerosols produced from ECs.[22] Strict guidelines exist for testing of leachables and extractables in metered dose inhalers (MDIs) and nebule ampoules. However, this information for e-liquids is largely unknown due to the lack of regulation of these products.

How do ECs compare with pharmaceutical inhaler products?

The major difference between ECs and conventional pharmaceutical inhaler products is that, in ECs, thermal vaporization is required to form the aerosol. In this respect, they are similar to the Staccato® delivery system (Alexza Pharmaceuticals, Mountain View, CA, US), in which a drug pre-coated onto a solid substrate surface is rapidly heated upon inhalation by the patient.[41] The vaporized drug condenses into an aerosol due to cooling while traveling through the mouthpiece. However, ECs also differ from the Staccato system in that they contain a range of GRAS—but not fully tested excipients—while the Staccato system is excipient-free. Furthermore, formulations for ECs are liquid solutions, whereas for the Staccato system, the formulation is a solid. As mentioned, well over 90% of the nicotine, glycerin and propylene glycol inhaled from a range of ECs were systematically absorbed.[29] The Staccato single dose delivery system is also very efficient, emitting ≥ 91% of the loaded dose of loxapine, with only about 11% of the emitted dose depositing consistently in the oropharyngeal region, when tested at airflow rates of 15-80 L/min *in vitro*.[41] That means about 89% of the emitted dose should deposit in the lungs. Nicotine has also been successfully delivered from a Staccato system, although this product has not been commercialized.[42] Since nicotine is a liquid under ambient conditions, it cannot form a physically stable film on the substrate. Therefore, it was chemically combined with thermally reversible zinc halides ($ZnBr_2$ and $ZnCl_2$) to form molecular complexes that can be loaded as solid coatings. Highly pure aerosols containing 99% nicotine could be generated with an emitted dose of 116.8 μg, of which 57% was droplets with a volumetric mean diameter of 800 nm and 43% was vapor.[42] The small droplet size indicated that they can deposit in the deep lungs. It should be noted the Staccato system requires a much higher airflow rate than ECs to emit an aerosol (15-80 L/min vs. 1-3 L/min). If we compare aerosol performance in the light of this, ECs are much more efficient because they require much lower inhalation effort by the patient to actuate the dose. This property is beneficial in pulmonary drug delivery because inhalation effort can be adversely affected by the disease state, such as that in asthma.

Two EC-like products have been approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) for nicotine replacement therapy, namely the Voke Inhaler and e-Voke Electronic Inhaler (Kind Consumer, London, UK). The Voke Inhaler is a breath-actuated MDI in the shape of an EC containing nicotine. It uses the propellant HFA-134a to provide the energy for aerosol generation.[43] Unlike ECs, no heating is involved in the Voke Inhaler. Besides the propellant, it includes propylene glycol, ethanol, saccharin and levomenthol as excipients.[43] This product was deemed to be therapeutically equivalent to the reference product, Nicorette® Inhalator.[43] Unlike the Voke Inhaler, the e-Voke Electronic Inhaler is actually an EC in its design and operating

principle.[44, 45] Thus, it is the first EC that has been approved as a pharmaceutical product.[45] It uses a cartridge system containing a simple formulation, with glycerin and water as the vehicle.[44] The small number of excipients in the e-Voke formulation is probably in order to reduce the amount of likely thermal degradants. This product has also been demonstrated to be therapeutically comparable to Nicorette Inhalator.[44]

Future directions

The e-Voke Electronic Inhaler shows it is possible to apply EC technology in the pharmaceutical field. It would be interesting to consider the possibility of using these devices with other inhaled drugs for treating local and systemic diseases. Also, the use of propylene glycol and glycerin in the two formulations discussed above opens the possibility of their more widespread use as excipients for inhaled products. ECs have the advantage of generating fine droplets at low airflow rates, which are ideal for patients. However, the heating mechanism would limit formulation ingredients (actives and excipients) to those that are thermal-stable. Furthermore, the long-term health effects of inhaled EC aerosols, especially those containing flavoring agents, also need to be monitored. Besides these major points, many aspects of ECs have not been studied extensively, e.g., site of deposition and absorption *in vivo*, mode of aerosolization (droplet vs. vapor fractions), delivery mechanism and effect of physicochemical parameters of the formulation. Much useful knowledge on these topics can be gained by inhalation technologists that may lead to the application of EC technology for novel inhalation therapies.

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Philip Chi Lip Kwok (corresponding author) is an Assistant Professor of the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong SAR, Tel.: +852 3917 6335, pclkwok@hku.hk. Philippe Rogueda is the Executive Director of Aedestra Limited, 16 D & E, Neich Tower, 128 Gloucester Road, Wanchai, Hong Kong SAR. Lu Hou is a Master of Medical Sciences student of the Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong.